WPDP™
Washington Prescription Drug Program
Administered by the Washington State Health Care Authority
A member of the Northwest Prescription Drug Consortium

Date: **December 19, 2012**

Benign Prostatic Hypertrophy Disease State Review

Significant events since Feb 2003

- **Drug Approvals**
  - **October 2008:** Rapaflo (silodosin) for the treatment of signs and symptoms of benign prostatic hyperplasia.
  - **June 2003:** Uroxatral (alfuzosin) for the treatment of signs and symptoms of benign prostatic hyperplasia.

- **New Indications**
  - **October 2011:** the US Food and Drug Administration (FDA) approved tadalafil (Cialis®; Eli Lilly and Company; Indianapolis, Indiana) for benign prostatic hyperplasia (BPH) and erectile dysfunction with signs and symptoms of BPH.
  - **June 2008:** Avodart (dutasteride) in combination with alpha blocker, tamsulosin, is indicated for the treatment of symptomatic BPH in men with enlarged prostate.

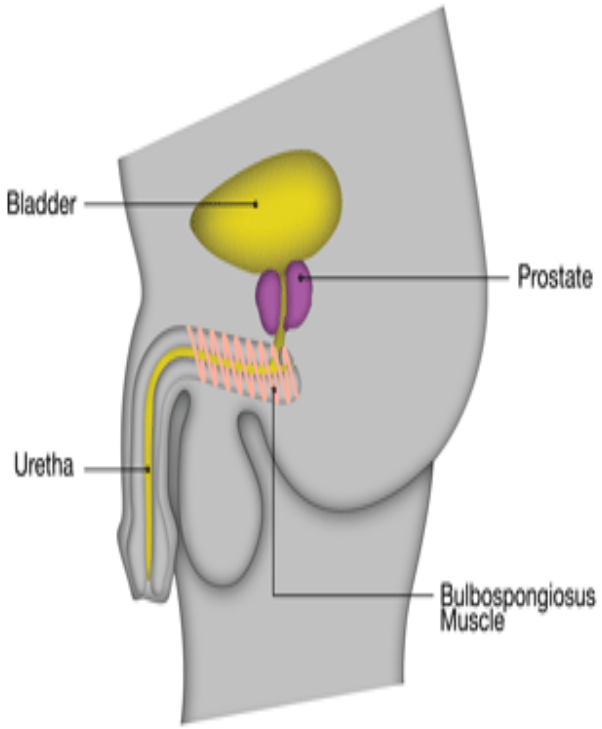
Background

- **Benign prostatic hypertrophy is an enlargement of the prostate that is sometimes accompanied by lower urinary tract symptoms (LUTS).**

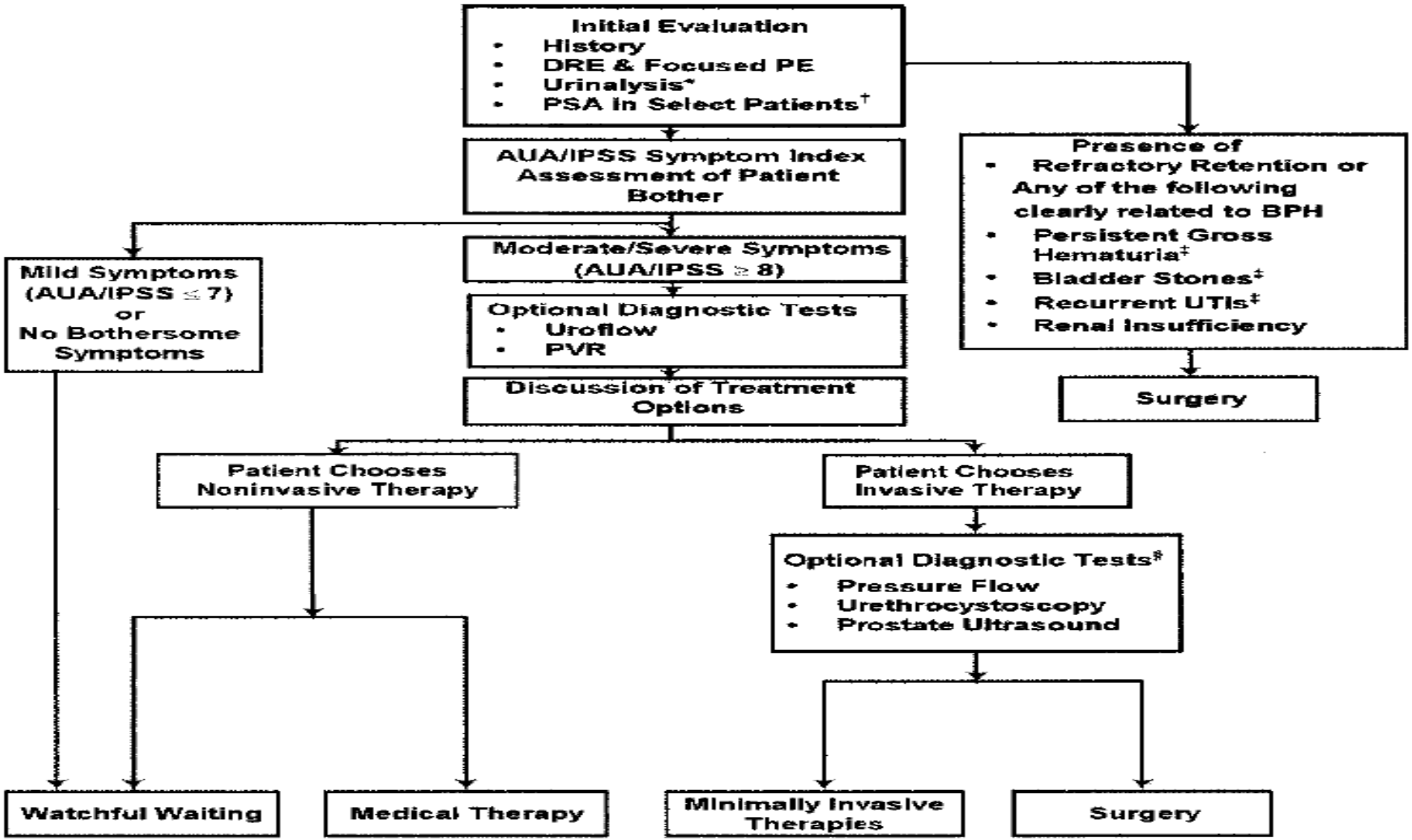
- Incidence of symptomatic BPH:
  - 20% > 40 years
  - 65% > 60 years
  - 90% > 70 years

Symptoms of BPH

- **Obstructive**
  - Hesitancy or straining
  - Weak stream
  - Incomplete bladder emptying
  - Intermittent stream
- **Irritative**
  - Frequency
  - Urgency
  - Incontinence



AUA BPH Management



AUA Symptom Index ~ IPSS

1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?
4. Over the past month or so, how often have you found it difficult to postpone urination?
5. Over the past month or so, how often have you had a weak urinary stream?
6. Over the past month or so, how often have you had to push or strain to begin urination?
7. Over the last month, how many times did you usually get up to urinate from the time you went to bed at night until the time you got up in the morning?

Never	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
◉	○	○	○	○	○
◉	○	○	○	○	○
◉	○	○	○	○	○
◉	○	○	○	○	○
◉	○	○	○	○	○
◉	○	○	○	○	○
◉ Never	○ 1 time	○ 2 times	○ 3 times	○ 4 times	○ 5 times or more

Madsen FA, Bruskewitz RC. Clinical manifestations of benign prostatic hyperplasia. Urol Clin North Am 1995;22:291-8

2003 AUA Treatment Guidelines

- Alpha-blockers:
  - Equally effective with slight differences in adverse-effect profiles
  - Prazosin and phenoxybenzamine are not recommended
  - AUA-SI improvement: -4 to -6 points

- 5α-Reductase Inhibitors:
  - Appropriate and effective treatments for patients with demonstrable prostatic enlargement
  - Shown to reduce risk of acute urinary retention and BPH-related surgery
  - AUA-SI improvement: -3 to -4 points

- Combination therapy may be appropriate with potential of additive benefits (doxazosin with finasteride and tamsulosin with dutasteride)

- Phytotherapy and other dietary supplements are not recommended

Goals of BPH Treatment

- **Relief of Lower Urinary Tract Symptoms (LUTS)**
- **Prevention of clinical progression and bladder decompensation**

Treatment Options for BPH

- **Non-Pharmacologic Therapy**
  - Concomitant drugs
  - Fluid regulation
  - Lifestyle changes
  - Dietary advice

- **Pharmacologic Therapy**
  - Alpha-adrenergic blockers
  - 5α-reductase Inhibitors
  - Phytotherapy

- **Surgery**
  - Minimally invasive therapies
    - Transurethral microwave procedures
    - Transurethral needle ablation (TUNA)
    - High-intensity focused ultrasound (HIFU)
  - Transurethral resection of the prostate (TURP)
  - Open Prostatectomy

Indications

Drug	BPH: Urinary symptoms	BPH: Combination with alpha blocker	Hyper-tension	Alopecia	Radiation-induced urethritis	Ureteric stone	Noc-turia	Px of Prostate CA	Hirsutism	Chronic pelvic syndrome
Alpha-adrenergic Blockers										
Cardura (doxazosin)	X		X		√	√				
Cardura XL (doxazosin)	X									
Minipress (prazosin)	√		X							
Hytrin (terazosin)	X		X		√		√			√
Flomax (tamsulosin)	X				√	√				
Uroxatral (alfuzosin)	X		√			√				
Rapaflo (silodosin)	X									
5-alpha Reductase Inhibitors										
Avodart (dutasteride)	X	X								
Proscar (finasteride)	X	X		X				√	√	√

X = FDA approved use; √ = Unlabeled use recognized in ASHP or DrugDex

Efficacy & Safety: Alfuzosin

- Roehrborn (2003) examined 3 similarly designed, randomized, double-blind, placebo-controlled trials (12 weeks in duration, n=473).
  - Change in IPSS: -6 vs. -4.2 points ($P < 0.005$)
  - Peak flow rates: 2.3 vs. 1.1 ml/s ($P < 0.001$)
  - Dizziness: 5.3% vs. 2.9%
  - Sexual adverse effects: 0.6%

- Nordling (2004) studied two doses of alfuzosin (10mg and 15mg) or tamsulosin once daily compared to placebo in a randomized, double-blind, multicenter trial (12 weeks in duration, n=625).
  - Change in IPSS:
    - alfuzosin 10mg: -6.5 (adjusted $P = 0.007$)
    - alfuzosin 15mg: -6 (adjusted $P = 0.050$)
    - tamsulosin 0.4mg: -6.5 (adjusted $P = 0.014$)
    - Placebo: -4.6
  - Dizziness:
    - alfuzosin 10mg: 6%
    - alfuzosin 15mg: 7%
    - tamsulosin 0.4mg: 2%
    - Placebo: 4%
  - Sexual adverse effects:
    - alfuzosin 10mg: 3%
    - alfuzosin 15mg: 1%
    - tamsulosin 0.4mg: 8%
    - placebo: 0%

Efficacy & Safety: Silodosin

- Kawabe (2006) compared silodosin 4mg, tamsulosin 0.2mg and placebo in a randomized, double-blind, and placebo-controlled trial (12 weeks in duration, n=176).
  - Change in IPSS:
    - Silodosin: -8.3
    - Tamsulosin: -6.8
    - Placebo: -5.3
  - Change in Qmax:
    - Silodosin: 3.31
    - Tamsulosin: 3.98
    - Placebo: 2.21
  - Adverse events (dizziness):
    - Silodosin: 88.6% (5.1%)
    - Tamsulosin: 82.3% (7.3%)
    - Placebo: 71.6% (4.5%)
  - Sexual effects (retrograde ejaculation):
    - Silodosin: 22.3%
    - Tamsulosin: 1.6%

Clinical Efficacy: Combination Therapy

- McConnell (2003) evaluated effect of monotherapy of doxazosin or finasteride versus combination therapy in 3,407 men with BPH (follow-up ~4.5 years)
  - Change in AUA-SI:
    - Placebo: -4
    - Doxazosin: -6
    - Finasteride: -5
    - Combination: -7
  - Risk reduction for clinical progression was nearly doubled in the combination therapy group vs. monotherapy groups.
    - Doxazosin: 39%
    - Finasteride: 34%
    - Combination: 66%
- Roehrborn (CombAT trial, 2008) assessed two-year results from an ongoing 4-yr study on 4,844 men with moderate to severe BPH symptoms (IPSS ≥12, prostrate volume ≥30cc) to compare the effects of tamsulosin 0.4mg, dutasteride 0.5mg, or both.
  - Change in IPSS:
    - dutasteride: 4.9
    - tamsulosin: 4.3
    - Combination: 6.2

Safety Considerations

- Adverse effects commonly seen in alpha-blockers include dizziness, headache, asthenia, postural hypotension, rhinitis, and sexual dysfunction (retrograde ejaculation) in 5% - 9% of patient population.
- The most common adverse effect seen with alfuzosin was dizziness (~5%); syncope, hypotension, sexual dysfunction were rare.
- The most common adverse effect seen with silodosin was abnormal or retrograde ejaculation (22% vs. 2% with tamsulosin, 0% with placebo)
- Both tamsulosin and silodosin have been associated with intraoperative floppy iris syndrome (IFIS).
- Dutasteride and finasteride have been associated with decreased libido, erectile dysfunction, and inhibition of developing fetus.

Conclusions

- Literature does not suggest superiority, in terms of efficacy or effectiveness, amongst alpha-blockers.
- Newer alpha-blocking agents, alfuzosin and silodosin have minimal advantages. Alfuzosin may have less sexual side effects.
- Terazosin and non-selective alpha-blockers have more side effects, mainly related to hypotension.
- Direct comparisons of dutasteride with finasteride are lacking, more studies are needed to evaluate superiority; no evidence that dutasteride offers any advantage over finasteride
- 5α-Reductase Inhibitors are slower to relieve BPH symptoms than alpha-blockers but has been shown to reduce the risk of acute urinary retention and surgical intervention
- Combination therapy may relieve BPH symptoms more quickly than monotherapy for patients with enlarged prostate volume and double the risk reduction of clinical progression

Questions?